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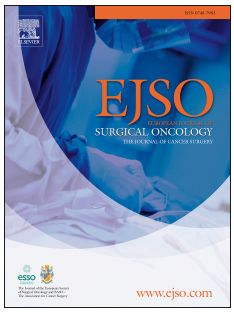

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TITLE

The impact of pre- and post-operative weight loss and body mass index on prognosis in patients with oesophageal cancer

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Abstract

Background: Weight loss is a cardinal symptom of oesophageal cancer and is often continued after surgery. High body mass index (BMI) is a strong risk factor for oesophageal adenocarcinoma. This study aimed to assess the impact of pre- and post-operative weight loss and BMI on long-term mortality after resection for oesophageal cancer.

Methods: This prospective and nationwide cohort study included 390 patients, operated on for oesophageal cancer in Sweden in 2001-2005 with follow-up until 2016, who responded to a questionnaire on weight history 6 months after surgery. Multivariable Cox proportional hazard models provided hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality while adjusting for several prognostic factors, including tumour stage.

Results: Compared to weight stable patients, pre-surgery weight loss indicated increased HRs of overall all-cause mortality (HR=1.32, 95% CI 0.94-1.86) and disease-specific mortality (HR=1.36, 95% CI 0.93-1.98). Patients with >20% weight loss post-surgery had worse overall all-cause mortality (HR=1.71, 95% CI 1.01-2.88) and disease-specific mortality (HR=2.20, 95% CI 1.24-3.89). Compared to patients with normal BMI, decreased HRs were indicated for patients who were obese at the time of surgery (overall all-cause mortality HR 0.87 95% CI, 0.58-1.31 and disease-specific mortality HR=0.89, 95% CI 0.57-1.40), while patients with BMI ≤19.9 at 6 months post-surgery had increased all-cause mortality (HR=1.41, 95% CI 1.03-1.95) and disease-specific mortality (HR=1.55, 95% CI 1.09-2.21).

Conclusion: Post-operative weight loss and low BMI at 6 months post-surgery are independent markers of poor prognosis in patients who undergo surgery for oesophageal cancer.

Keywords

Oesophageal neoplasm; weight change; BMI; survival; mortality.

INTRODUCTION

Oesophageal carcinoma is the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide[1]. The overall 5-year survival rates are poor (<20%)[2] and the incidence of adenocarcinoma of the oesophagus is increasing rapidly[3]. High body mass index (BMI) is a well-recognised risk factor for adenocarcinoma of the oesophagus[4, 5]. Weight loss is a common (57-83%) presenting symptom of oesophageal cancer[6, 7]. Dysphagia, reduced oral intake, and altered nutrient metabolism associated with systemic inflammation induced by the tumour, can all contribute to this weight loss and malnutrition[6-8]. Surgery is the mainstay of curative treatment for patients diagnosed with locally advanced oesophageal cancer[9]. Malnutrition is associated with increased post-operative morbidity and mortality after gastrointestinal surgery[10-12]. Some research indicates that pre-operative weight loss of >10% is associated with reduced overall 5-year survival after surgery for oesophageal cancer[13]. Continued weight loss and malnutrition are also common after surgery; post-surgery weight loss is seen in most patients, and is often profound and long-lasting[14, 15]. However, the impact of post-surgery weight loss on long-term survival has not been explored. The aim of this study was to assess the impact of pre- and post-operative weight loss and BMI on long-term survival after resection for oesophageal cancer.

PATIENTS AND METHODS

Design

This was a prospective nationwide cohort study in Sweden, which builds on a long-lasting and all-encompassing research network of hospital departments and clinicians with an interest in oesophageal cancer established in the 1990s[16]. During the period 2001-2005,

90% of all surgically treated patients with oesophageal cancer in Sweden were included and the participants were followed up regularly post-operatively until February 2016. The principles and organisation of the nationwide data collection have been described elsewhere. The ethics committee at the Karolinska University Hospital, Karolinska Institutet, Sweden, approved the study; reference numbers: 01-064, date: 2001-02-05; 01-340, date: 2005-12-29; 05/1491-32, date: 2005-12-29. Data regarding patient and tumour characteristics, hospital stay, surgery and complications were collected prospectively through continuous manual scrutiny of medical records. An extensive study protocol was completed by the study researchers for each patient, ensuring uniformity. Tumour stage was classified according to the International Union Against Cancer[17]. Mortality was determined by linkage to the 100% complete Swedish Register of the Total Population[18]. Data on weight changes were collected through written study-specific questionnaires assessing height and average weight as adults, weight just before operation, and weight at 6 months after surgery[15]. Patients who responded to this questionnaire were eligible for this study.

Exposures

The study exposures were weight changes and BMI at defined time points in relation to surgery. Weight changes were evaluated in three categories: 1) between the average weight as an adult and weight at time of operation ('Pre-operative weight change'); 2) between the time of surgery and 6 months following surgery ('Post-operative weight change'); and 3) between the average weight as an adult and weight at 6 months after surgery ('Pre-operative to post-operative weight change'). Weight changes were categorised into four groups: 1) Weight gain or stable weight (+/-1.0%); 2) 1.1-10.0% weight loss; 3) 10.1-20.0%

weight loss; and 4) >20.0% weight loss. BMI (body weight in kilograms (kg) divided by the square of the body height in metres (m) [kg/m^2]) was assessed at two time points: 1) at operation and 2) at 6 months post-surgery. BMI was categorised into four groups: ≤19.9 ('low'), 2) 20.0-24.9 ('normal'), 3) 25.0-29.9 ('overweight'), and 4) ≥30.0 ('obesity').

Outcomes

All-cause and disease-specific mortality was measured in days after surgery and assessed as 6 months to end of study period (February 2016) and 6 months to 5 years. The follow-up from 6 months was because patients had to have survived for at least 6 months after their surgery to respond to the weight history questionnaires. All-cause mortality was defined as death from any cause during follow-up in the Swedish Causes of Death Registry[18]. Disease-specific mortality was defined as a death where oesophageal cancer was recorded as a cause of death during follow-up in the Causes of Death Registry[18].

Statistical analysis

Kaplan Meyer survival curves were plotted and compared with the log rank test. Cox proportional hazard models were calculated to assess the hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality associated with weight change and BMI. All HRs were adjusted for the following nine potential confounding factors: 1) age (continuous variable), 2) sex (male or female), 3) comorbidity (categorised into 0, 1 or ≥2 according to the Charlson Index Scoring System)[19], 4) neoadjuvant therapy (yes or no), 5) tumour stage (0-I, II, III or IV), 6) placement of a feeding jejununostomy (yes or no), 7) surgical approach (oesophagectomy, extended total gastrectomy or oesophagogastrectomy), 8) histological type of tumour (adenocarcinoma or squamous-cell carcinoma), and 9) education (≤9, 10-12,

or >12 years of formal education). Additionally, the HRs evaluating post-operative weight change were further adjusted for pre-operative weight change, the HRs of BMI at operation were further adjusted for pre-operative weight change, and the HRs of BMI at 6 months were further adjusted for pre to post-operative weight change. Pre-operative, post-operative and pre to post-operative (total) weight changes were categorised into weight gain or stable weight [+/-1%]; 1.1-10% weight loss; 10.1-20.0% weight loss; and >20.0% weight loss). Trend tests were performed to assess any linear trends in weight changes with respect to the study outcome using contrasts.

Results

Patients

Of the entire cohort including 616 patients, 506 survived for at least 6 months and were thus eligible for this study. Among these, 402 answered the questionnaire about height and weight (79.4% response rate). Out of 402 patients 12 patients were removed due to missing information on weight loss or confounders. The remaining 390 patients were included in the present study. Characteristics of the study participants are presented in Table 1. There were more men (80.8%) than women, the average age was 65.6 years, and most patients had no comorbidity (57.7%). Tumour stage III (40.3%) was more common than other stages, and adenocarcinoma was the most common histological tumour type (75.9%). Few patients (6.4%) had received neoadjuvant therapy, a majority underwent oesophagectomy (79.7%) with clear resection margins (91.0%), and a feeding jejunostomy was inserted in 44.6% of patients (Table 1).

Pre-operative weight loss and risk of mortality

As presented in Table 2, a majority (56.9%) of patients experienced weight loss before surgery. Pre-operative weight loss indicated increased point HRs of mortality, but these were not statistically significant (Table 2). The highest HR was found for disease-specific overall mortality among patients who had lost 10.1-20% of their weight before surgery (HR 1.36, 95% CI 0.93-1.98). No clear trends with increased weight loss were found (Table 2).

Post-operative weight loss and risk of mortality

A large proportion of patients lost weight after surgery (86.9%) (Table 2). Patients with weight loss of >20% had an increased mortality compared to patients who were weight stable (all-cause overall mortality HR 1.71, 95% CI 1.01-2.88; disease-specific 5-year mortality HR 2.00, 95% CI 1.12-3.57; and disease-specific overall mortality HR 2.20, 95% CI 1.24-3.89). There were statistically significant trends towards increased disease-specific mortality in patients who lost weight (Table 2).

Pre-operative to post-operative weight change and risk of mortality

Most patients (95.5%) lost weight from before the disease to 6 months after surgery, the majority of whom (74.5%) lost >10%. Patients with weight loss of >20% had strongly increased HR of mortality compared to patients who were weight stable (disease-specific 5-year mortality HR 2.83, 95% CI 1.00-8.02; disease-specific overall mortality HR 3.29, 95% CI 1.17-9.29) (Table 2). There was also a statistically significant trend towards increased overall disease-specific mortality for patients who lost weight (p=0.03).

BMI at operation and risk of mortality

The largest group of patients (40.6%) had a BMI within the normal range (20-24.9) at the time of surgery. A low BMI of ≤19.9, was seen in 10.3% of patients. Compared to patients with a normal BMI, there was no increased HRs of mortality in patients who were underweight, overweight or obese (Table 3). However, there were statistically non-significantly decreased HRs for the BMI ≥30 category (Table 3).

A sub analysis was undertaken to assess mortality in patients with a high pre-operative BMI (BMI ≥25) and high post-operative weight loss (≥20%) compared to patients with a pre-operative BMI <25 and <20% post-operative weight loss. Having a high pre-operative BMI and high post-operative weight loss indicated increased point HRs of mortality (disease-specific 5-year mortality HR 1.20 95% CI 0.79-1.81; disease-specific overall mortality HR 1.38 95% CI 0.92-2.07), but these were not statistically significant.

BMI at 6 months after surgery and risk of mortality

The proportions of patients with a normal BMI and with a BMI ≤19.9 at 6 months after surgery were 53.7% and 25.3%, respectively. Conversely, the proportions of patients within the overweight and obese categories were reduced to 18.9% and 2.1%, respectively. Patients with a low BMI (≤19.9) had higher all-cause and disease-specific HRs of mortality compared to patients with a normal BMI (Table 3). Compared to patients in the normal range of BMI, those who had a BMI of ≤19.9 had a HR of disease-specific 5-year mortality of 1.66 (95% CI 1.16-2.38). The HRs for the BMI ≥30 category were non-significantly decreased (Table 3).

A sensitivity analysis excluding patients (n=35, 9.0%) with non-radical resection margins (R1/2) did not change the HRs for any of the exposures or outcomes (data not shown).

Discussion

In this study, weight loss after surgery and low BMI (≤19.9) at 6 months post-surgery were independent and statistically significant poor prognostic indicators in patients who underwent surgery for oesophageal cancer, while pre-operative weight loss of >10% might also increase mortality. Having a BMI ≥30 before or after surgery may be a good prognostic factor.

Strengths of this study include its prospective and population-based design with inclusion of unselected patients undergoing cancer surgery, with high questionnaire response rate. Other strengths are the large sample size, the high national coverage, the complete and long follow-up and the adjustment for several potential confounding factors. The detailed and prospective data collection and the objective manual review of each case record including evaluation of internal validity ensured high validity of the collected data. The self-reported data on weight and height is a potential weakness. However, the weight of these patients is typically objectively measured repeatedly from before surgery and at clinical follow-ups, making it likely that the reported measures were in fact accurate in most patients. Patient-reported height, weight and weight change history have been shown to be reliable[20, 21]. A study from the same cohort validated self-reporting of weight [20], showing a correlation coefficient of 0.77, indicating good correlation. Another limitation is that patients who did not survive 6 months after surgery were not included. This may have mitigated the impact of mortality associated with post-operative complications on survival. However, it is unlikely that the associations found in this study would have been weaker if early post-operative deaths were also included, but rather the opposite. Finally, the lack of details around pre-

operative weight loss, in terms of the time frame and whether the weight loss was unintentional or not, may have affected the results of the pre-operative and total weight changes analysis.

Malnutrition is a common condition after surgery for oesophageal cancer[15, 20, 22]. Yet, the impact of post-operative malnutrition on survival has been poorly studied. The present study showed a strong and dose-response association between increasing weight loss and increased mortality. In a study of 1-year survivors (*n=205*) after transthoracic oesophagectomy for cancer, a ≥10% weight loss had an independent negative prognostic impact on disease-free survival[23]. Previous studies which found reduced survival associated with weight loss attributed this to those patients who lost weight receiving less chemotherapy[24, 25]. However, the majority of patients in the present cohort (93.6%) did not receive perioperative oncological treatment. The results were adjusted for tumour stage to assess if the association between weight loss and mortality was a reflection of a more advanced tumour; however this was not the case.

Malnutrition is associated with compromised immunity[26]. The immune system is the body's primary defence against cancer cells[27]. Tumours are recognised by the immune system and their development can be stopped or controlled long term through a process known as immunosurveillance[28]. Therefore, this could be a factor in earlier disease recurrence in patients who lose weight. Also, the survival advantage seen in the patients who are obese might be associated with their greater nutritional reserve.

The HRs of this study indicated that pre-operative weight loss >10% increased the mortality independent of other factors, although no statistically significant association was shown.

The aforementioned study weaknesses in relation to the exclusion of patients who did not survive 6 months after surgery and the lack of detail around the weight loss could have diluted these results. Several other studies have reported that pre-operative weight loss of >10% increases the risk of mortality after oesophageal cancer surgery[13, 29, 30]. Another study found that >2% pre-operative weight loss was an independent predictor of reduced 5-year survival in patients after oesophagectomy[31]. Weight changes in the current study were classified into 4 categories to investigate if there were any differences in the impact on survival of weight loss at various rates with the aim of providing insight to aid clinical decision-making.

Our study demonstrated that being obese at the time of surgery and at 6 months post-surgery is a possible good independent prognostic factor, although this was not statistically significant. A survival benefit with having a high BMI has been reported in some studies examining pre-surgery BMI and survival in oesophageal cancer[32, 33], whilst others have found the effect equivocal[34, 35]. Comparison however with other literature was difficult due to the differing classifications of BMI used, often dichotomous classifications of </> 30 or </> 25 [33-35]. We used the World Health Organisation's (WHO) classification of BMI[36] with the exception of the underweight category, which was classified as ≤19.9 instead of <18.5. Having a BMI <20 is considered to be malnourished if accompanied with 5% unintentional weight loss[37] which was the rationale for using the cut off ≤19.9.

It would seem clear that interventions to minimise weight loss before and after surgery have the potential to improve survival. Jejunostomy feeding tubes are often used to feed patients after surgical resection for oesophageal cancer, with some patients continuing jejunostomy

feeding at home[38]. A study from our group indicated a reduced risk of weight loss in the patients who had a jejunostomy[39]. Therefore, presence of jejunostomy tubes was adjusted for in the current study; this was not found to be a confounder or mediator of the associations reported. Jejunostomy feeding tubes are not without risk of serious complications[40]. With an increasing focus on survivorship, and developments in symptom management, jejunostomy feeding tubes may not be the optimal intervention for many patients. Further research is needed to substantiate the benefits of jejunostomy feeding over intensive dietary counselling and support along with symptom management, and to determine optimum patient selection. Indeed jejunostomy feeding would need to be considered as part of a multimodal approach to counteract weight loss rather than in isolation, as it is becoming increasing evident that loss of muscle mass, or sarcopenia, is likely to be more of a confounding factor on survival than simply weight loss.

Sarcopenia is prevalent in patients with oesophago-gastric cancer before surgery and has been shown to be associated with chemotherapy dose limiting toxicity and with poorer survival[41, 42, 43, 44, 45]. The patients in this study with postoperative weight loss and low BMI (≤19.9) may be considered potentially sarcopenic, contributing to their higher risk of mortality.

Given the complexity of factors which affect nutritional status, integrated multimodal approaches to intervention would seem appropriate. With the prevalence of malnutrition increasing from diagnosis into survivorship and considering the impact this has on outcomes, it would seem paramount that interventions should be implemented with the aim of prevention rather than reversal, in order to prevent weight loss surpassing that level

beyond which the detriment occurs. Further research evaluating the impact of surgery on body composition and its implications on survival would be valuable. Interventions which may mitigate the impact of treatment on skeletal muscle mass, such as physical activity and nutrition, should be a key consideration of any prehabilitation and rehabilitation programs.

In conclusion, this nationwide population-based cohort study with adjustment for known prognostic factors indicates that post-operative weight loss and low BMI (≤19.9) at 6 months post-surgery are independent poor prognostic indicators in patients who undergo surgery for oesophageal cancer. Pre-operative weight loss >10% was shown to be potentially hazardous, while being obese before and after surgery may infer a survival benefit. Early and timely interventions to prevent or minimise malnutrition in this group of patients has the potential to improve prognosis.

Conflicts of Interest:

The authors declare no conflicts of interest.

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Table 1: Characteristics of patients who underwent surgery for oesophageal cancer.	
Age (mean, in years)	65.6
	Number (%) of patients
Gender	
Male	315 (80.8)
Female	75 (19.2)
Education	
Nine-year compulsory	181 (46.4)
Upper Secondary	152 (39)
Higher Education/Degree	57 (14.6)
Charlson comorbidity score	
0	225 (57.7)
1	95 (24.4)
≥2	70 (17.9)
Tumour stage (post-operative)	
0-I	82 (21.0)
II	119 (30.5)
III	157 (40.3)
IV	32 (8.2)
Tumour histology	
Adenocarcinoma and dysplasia	296 (75.9)
Squamous cell carcinoma	94 (24.1)
Neoadjuvant chemotherapy received	
Yes	25 (6.4)
No	365 (93.6)
Surgical approach	
Oesophagectomy	311 (79.7)
Extended total gastrectomy	40 (10.3)
Oesophagogastrectomy	39 (10.0)
Resection margin status	
Radical (R0)	355 (91.0)
Non-radical (R1/2)	35 (9.0)
Placement of a feeding jejunostomy	
Yes	174 (44.6)
No	216 (55.4)

Table 2: Perioperative weight changes in patients with oesophageal cancer and risk of mortality, presented as hazard ratio (HR) with 95% confidence interval (CI) [a]

		All-cause mortality						Disease-specific mortality					
		Within 5 years of surgery			Overall			Within 5 years of surgery			Overall		
Pre-operative weight change	**Number (%)** [b]	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**
Stable/gain (+/-1%)	153 (43.1)	1.00	reference		1.00	reference		1.00	reference		1.00	reference	
1.1-10%	116 (32.7)	0.85	0.62-1.17		0.84	0.63-1.14		0.79	0.56-1.12		0.79	0.57-1.11	
10.1-20%	57 (16.0)	1.26	0.87-1.81		1.32	0.94-1.86		1.33	0.91-1.97		1.36	0.93-1.98	
>20%	29 (8.2)	1.19	0.74-1.92	0.23	1.10	0.69-1.76	0.31	1.18	0.72-1.94	0.20	1.04	0.64-1.69	0.39
Post-operative weight change at 6 months	**Number (%)** [b]	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**
Stable/gain (+/-1%)	50 (13.1)	1.00	reference		1.00	reference		1.00	reference		1.00	reference	
1.1-10%	97 (25.4)	1.20	0.75-1.93		1.28	0.82-2.00		1.28	0.78-2.11		1.45	0.89-2.37	
10.1-20%	162 (42.4)	1.24	0.77-1.99		1.21	0.78-1.90		1.35	0.82-2.22		1.29	0.80-2.09	
>20%	73 (19.1)	1.70	0.98-2.95	0.06	1.71	1.01-2.88	0.06	2.00	1.12-3.57	0.02	2.20	1.24-3.89	0.01
Pre-operative to post-operative weight change (total)	**Number (%)** [b]	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**	**HR**	**95% CI**	***P* for trend**
Stable/gain (+/-1%)	16 (4.5)	1.00	reference		1.00	reference		1.00	reference		1.00	reference	
1.1-10%	74 (21.0)	1.59	0.66-3.79		1.55	0.72-3.34		1.90	0.66-5.50		2.07	0.72-5.94	
10.1-20%	168 (47.6)	1.31	0.57-3.04		1.31	0.63-2.74		1.58	0.57-4.44		1.87	0.68-5.21	
>20%	95 (26.9)	2.10	0.90-4.92	0.12	2.03	0.96-4.28	0.09	2.83	1.00-8.02	0.07	3.29	1.17-9.29	0.03

[a]Results adjusted for age, sex, education, co morbidity, tumour stage, tumour histology, pre-operative weight change in the analysis of post-operative weight change, neoadjuvant chemotherapy received, surgical approach and presence of a jejunostomy. [b]Number of patients not adding up to 390 patients represent missing data.

Table 3: Perioperative body mass index (BMI) in patients having surgery for oesophageal cancer and risk of mortality, presented as hazard ratio (HR) with 95% confidence interval (CI) [a]

		All-cause mortality				Disease-specific mortality			
		Within 5 years of surgery		Overall		Within 5 years of surgery		Overall	
BMI at operation	**Number (%)**[b]	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
≤19.9	39 (10.3)	1.05	0.64-1.72	1.01	0.63-1.64	1.02	0.60-1.74	1.07	0.62-1.85
20-24.9	153 (40.6)	1.00	reference	1.00	reference	1.00	reference	1.00	reference
25-29.9	121 (32.1)	1.15	0.82-1.61	1.15	0.84-1.58	1.04	0.72-1.50	1.08	0.76-1.53
≥30	64 (17)	0.83	0.53-1.31	0.87	0.58-1.31	0.80	0.50-1.27	0.89	0.57-1.40
BMI at 6 months post-surgery	**Number (%)**[b]	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
≤19.9	95 (25.3)	1.51	1.08-2.11	1.41	1.03-1.95	1.66	1.16-2.38	1.55	1.09-2.21
20-24.9	202 (53.7)	1.00	reference	1.00	reference	1.00	reference	1.00	reference
25-29.9	71 (18.9)	0.90	0.60-1.33	0.79	0.54-1.14	0.93	0.61-1.40	0.87	0.58-1.29
≥30	8 (2.1)	0.73	0.25-2.09	0.79	0.31-2.04	0.73	0.25-2.11	0.57	0.20-1.67

[a]Adjusted for age, sex, education, co morbidity, tumour stage, tumour histology, preoperative weight change in the analysis of BMI at operation, pre to post-operative weight change in the analysis of BMI at 6 months, neoadjuvant chemotherapy received, surgical approach and presence of a jejunostomy.

[b]Number of patients not adding up to 390 patients represent missing data.